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Viewpoint

Recent updates in diagnosis and management of drug-resistant tuberculosis in India: A paradigm shift and the way ahead during the COVID-19 crisis

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ABSTRACT

The recent guidelines on the Programmatic Management of Drug-Resistant Tuberculosis (DR-TB) in India (PMDT) have been released in March 2021 on World TB Day. The new guidelines have considered emerging diagnostic trends including TrueNat, Xpert Mtb/XDR, Next generation sequencing and evaluation for resistance to newer drugs including Bedaquiline (Bdq) and Delamanid. The emerging therapeutic trends include focus on oral shorter Bdq based regimen with phasing out injectables use. The replacement sequence of drugs for DR-TB have also been updated. Updated definitions for pre-XDR, XDR, culture conversion and default have also been added. These guidelines are a paradigm shift which will make treating DR-TB easier and more efficient especially during the ongoing COVID-19 pandemic crisis.

1. Introduction

India has the highest burden of tuberculosis (TB) in the world, having an estimated incidence of 2.7 million cases in 2019.[1] This crisis evokes a deeper concern considering the increasing proportion of drug-resistant TB (DR-TB) cases. India had an estimated 130,000 DR-TB cases in 2018, while the estimated percentages of new cases and previously treated cases with multidrug-resistant (MDR) or rifampicin-resistant (RR) TB in 2017 were 2.8% and 12% respectively. As per the National Drug Resistance Survey (NDRS) released in 2018, only 44% of the estimated MDR-TB cases were diagnosed and almost 65% of the cases remained untreated.[1] The increasing burden of DR-TB has led to the rapid expansion of Programmatic Management of Drug Resistant Tuberculosis (PMDT) services in recent times. Endorsed by the World Health Organization (WHO) in 2002, India adopted the PMDT services in 2007 and complete geographic coverage was achieved in 2013. Since then, PMDT, a comprehensive document on diagnosis and treatment of DR-TB is updated regularly anticipating the current needs in providing for the DR-TB services.

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The latest guidelines on management of DR-TB have been released on 24th March 2021, the World TB Day. The new document incorporates emerging diagnostic and therapeutic trends, while focussing on the elimination of TB under the National TB elimination program (NTEP).[1] In order to achieve the sustainable development targets by 2025 (i.e., five years before 2030, the global target year), the national strategic plan (NSP) 2017-25 emphasizes on the 'prevent-detect-treat-build' strategy. The PMDT-2021 guidelines are a welcome step, with the updated recommendations backed by the evolving evidence and are in coherence with the WHO technical report.[2] The update spans from definitions and diagnostics; to treatment and logistics. The main driving force behind majority of the suggested changes in these guidelines is the current evidence regarding the promising efficacy of the two newest members of the antitubercular treatment (ATT), i.e., Bedaquiline (Bdq) and Delamanid (Dlm).

2. Changes in diagnosis of DR-TB

The WHO recently revised the definition of extensively drug-resistant tuberculosis (XDR-TB), who have also defined pre-XDR-TB for the first time, highlighting the seriousness of these forms of TB. XDR and Pre-XDR TB are defined on the basis of resistance to certain key drugs. The WHO had issued an updated interim guidance in 2019 which re-classified anti DR-TB drugs into three categories (A, B, and C).[2] The update was based on evidence of the high effectiveness of levofloxacin/moxifloxacin, Bdq, and linezolid in DR-TB. The PMDT- 2021 India update has now officially adopted this new classification. The drugs which form Group-A, are the key pillars on which the new PMDT regimens stand. Since these key pillars have evolved, and the second-line injectable drugs (SLIDs) are given less importance now, these definitions have also been changed appropriately. New definitions for pre-XDR and XDR-TB aim to define more precisely the groups of TB patients who require complex treatment regimens. The (SLID) resistance-based criteria for the diagnosis of Pre-XDR/XDR TB have been removed.[1] Pre-XDR TB is now defined as Multidrug-resistant/rifampicin-resistant (MDR/RR) TB with FQ resistance. XDR-TB is now defined as Pre-XDR TB with additional resistance to Bdq and/or linezolid. These new definitions are not only expected to lead to better reporting, surveillance and monitoring of DR-TB, but also, stimulate the development of better treatment regimens for these dangerous forms of TB.

PMDT-2021 also focuses on the challenges with the available diagnostic modalities for DR-TB in India. CBNAAT (Xpert-Mtb) is a cartridge-based nucleic acid amplification test with a short turn-around time for diagnosing TB and at the same time, identifying rifampicin (R) resistance. This PCR-based test has managed to change the landscape of DR-TB diagnosis and treatment in our country. However, it requires an air-conditioner and uninterrupted power supply (UPS) for its functioning. These become a hindrance in many of the TB centres in remote areas of the country. The newer diagnostic modality, TrueNat is a chip-based test and is devoid of the above two liabilities, while maintaining the advantages offered by CBNAAT. The adoption of TrueNat in TB management may eventually prove to be a crucial step towards eliminating TB from the country. All samples that test positive in TrueNat, are further going to be subjected to TrueNat-MTB-Rif-Dx, to rule out rifampicin-resistance. Additionally, ruling out isoniazid- or fluoroquinolone-resistance by second line–line probe assay (SL-LPA) currently requires a turn-around time of at least 2 days. An advanced version of CBNAAT, the Xpert-Mtb/XDR can detect resistance against isoniazid (H), fluoroquinolones (FQs), SLIDs and ethionamide (Eto). The PMDT-2021 aims to progressively introduce this modality throughout the country. Xpert-Mtb/XDR will not only reduce turn-around times, but also lessen the excessive burden faced by the various centres which perform SL-LPA on samples from a large geographical area.

Currently, the Phenotypic Drug Susceptibility Testing (pDST) in India is available for R, H, Pyrazinamide (Z), FQs and SLIDs. The programme aims to commence Clofazimine (Cfz) pDST this year (2021).[1] Bedaquiline (Bdq) and Delaminid (Dlm) DST are currently available only at National Institute for Research in Tuberculosis (NIRT) and National Institute of Tuberculosis and Respiratory Diseases (NITRD). As the coverage of these drugs is expected to become incrementally more frequent, it is prudent to provide DST for these drugs to avoid a clinical or epidemiological crisis. These will soon be made available at other laboratories, providing greater access. Infrequent as it maybe, discordance of drug resistance results between genotypic and phenotypic DSTs is a potentially catastrophic clinical problem. In its technical report-2021, the WHO advised lowering the critical concentration in Mycobacteria Growth Indicator Tube (MGIT) based DST from 1 μg/ml to 0.5 μg/ml to reduce discordance between genotypic and phenotypic DSTs.[2]

Furthermore, the PMDT-2021 now explicitly recommends resolving discordance in RR between NAAT & first line–Line probe assay (FL-LPA) with a successively repeated NAAT.[3] Moreover, the pDST performed in MGIT can miss RR-TB associated mutations. Another new update has added for next generation sequencing (NGS) which can help in detection of genomic sequence variants[3] to predict TB drug-resistance phenotypes.

3. Changes in treatment of DR-TB

The treatment of DRTB rests on using all three key drugs (Group A), supplemented by one or both Group B drugs, to form a regimen of four or five total drugs. In the 2020 guidance, the WHO review group found similar success rates on using four, five or six drugs. The change in PMDT-2021 aligns with this. The focus has now clearly shifted away from SLID containing regimens. Citing the meta-analysis and trial data, the WHO re-classified anti DR-TB drugs. In view of the poorer outcomes with kanamycin and capreomycin, the WHO recommends avoiding these drugs. Amikacin, however, can be used as a Group-C drug, provided susceptibility to it has been confirmed. The focus now rests on an all-oral shorter regimen containing Bdq, in place of kanamycin containing (modified Bangladesh) regimen. The new Bdq-containing shorter oral regimen is recommended for all DRTB patients, provided there is no history of prior exposure to these drugs for 1 month or more, no resistance to FQ, and no extensive-TB defining

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presentation such as bilateral lung cavities, extensive parenchymal damage, miliary/meningeal/central nervous system TB, and/or any extrapulmonary TB in children except lymphadenopathy, children less than 5 years of age, pregnancy less than 32 weeks and lactation unless mother willing for formula feed. If any of the exclusion criterion is present, Bdq-containing longer oral regimens are used. The updated regimens are summarised in Table 1.

The evidence on shorter oral Bdq-regimen is primarily based on data from South Africa, which was reviewed by the WHO. The analysis of this standardized shorter regimen containing Bdq place of SLID, in combination with FQ, Cfz, High dose H, Ethambutol (E), Z and ethionamide (Eto) revealed a 13% higher treatment success rate of Bdq over SLID-regimen, with a treatment success rate similar to the conventional longer oral MDR-TB regimen. The change, which essentially replaces SLID with Bdq reduces the need for trained personnel for injection-administration and makes the all-oral regimen more accessible in remote and difficult-to-reach areas of the country. This along with the reduced pill burden, and consequently the adverse event durations associated with long term drug use, while achieving a treatment success rate comparable to the longer conventional regimen is likely to improve adherence and compliance to therapy. The new regimen has the potential of being a paradigm shifting change.

Regarding Bdq, the other important updates include the conditional approval for its use in ages 5–18 years, provided the body weight is above 15 kg and clearance by pediatrician has been obtained. Pregnant or lactating women, and stable-arrhythmia patients can also be prescribed Bdq based treatments. This is extrapolated from a recent study from South Africa which reported non-inferior treatment outcomes with the use of Bdq in pregnant or nursing mothers, and infants.[4] However, the decision to give Bdq must always be a concurrent decision of the obstetrician and physician weighing-in the risk-benefit ratio. Further, as ethionamide is contra-indicated in pregnancy up to 32 weeks of gestation, longer oral Bdq containing regimen should be used if the patient wants to continue with her pregnancy. However, if period of gestation is more than 32 weeks, the Bdq-containing shorter oral regimen is preferred. Lastly but equally importantly, Bdq can now also be used in Extra-pulmonary TB (EP-TB).

Delamanid (Dlm) can now be used in ages 6 years and above, in doses of 50 mg twice daily (6–11 years) and 100 mg twice daily (12 years and above). Recently, WHO has also stated that no extra safety concerns could be found for the concurrent use of Bdq and Dlm. These can be used together and even extended beyond 6 months if only 2 drugs are useable from groups A and B, and adequate group C drugs are not available or are contraindicated. Dlm requires no dose adjustments when used with antiretroviral therapy in patients of TB with human immunodeficiency virus infection (HIV).

The replacement sequence of drugs has also been updated in PMDT-2021 based on efficacy, resistance, adverse drug events, prior use, and background level of resistance. For H mono-/poly-resistance, FQs are to be used. If there is resistance to levofloxacin, then high dose moxifloxacin can be used, provided the susceptibility to the latter has been found. Else, the replacement order is linezolid (Lzd) followed by a combination of Cfz and cycloserine. Rifampicin is a key component in H-resistant TB regimens. However, it is decreases drug levels of Bdq. This precludes Bdq from being used in H-resistant TB. Dlm, Amikacin, Z, Eto is the recommended order, replacing the previous order (Z, A, Eto in 2019). The BPaL regimen (Bdq, pretomanid and Lzd) can also be used as a last resort in individualized settings since the evidence for this combination is still evolving.[5]

4. Other updates

The requirement of a DR-TB centre at every medical college has been stressed. The patient turn-around time has been updated and shortened. A digital e-Nikshay system for monitoring has been advocated. It has been shown that delay in referral to DR-TB centre is an important cause of delayed treatment initiation.[6] To improve the quality of care, a difficult-to-treat TB clinic (DT3C) is to be established at various state levels (Bihar and Maharashtra already have started). Benchmarks for turnaround time for CBNAAT (5–10 days),

Table 1 – Updated regimens for treatment of Drug-resistant Tuberculosis.

Clinical scenarios	Treatment duration and regimen
H mono/poly DR-TB regimen (R resistance not detected & H resistance detected)	(6 or 9 months) Lfx-R-E-Z
All MDR/RR-TB patients with no history of prior exposure to these drugs for 1 month or more, no resistance to FQ, and no extensive-TB defining presentation such as bilateral lung cavities, extensive parenchymal damage, miliary/meningeal/central nervous system TB, and/or any extrapulmonary TB in children except lymphadenopathy, children less than 5 years of age, pregnancy less than 32 weeks and lactation unless mother willing for formula feed.	(4–6 months) Bdq-Lfx-Cfz-Z-E-H-Eto followed by (5 months) Lfx-Cfz-Z-E
If any of the exclusion criterion is present, Bdq-containing longer oral regimens are used	
MDR/RR-TB patients who are excluded from shorter oral bedaquiline-containing MDR/RR-TB regimen including the XDR-TB patients.	(18–20 months) Lfx-Bdq-Lzd-Cfz-Cs (Bdq for six months or longer)

H: isoniazid; DR-TB: Drug-resistant tuberculosis; R: Rifampicin; Lfx: Levofloxacin; E: Ethambutol; Z: Pyrazinamide; MDR:Multidrug-resistant; RR: Rifampicin resistant; FQ: Fluoroquinolone; Bdq:Bedaquiline; Cfz:Clofazimine; Eto: Ethionamide; XDR:extensively drug-resistant; Lzd: Linezolid; Cs: Cycloserine.

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LPA (8–12 days) and culture-based DST (29–58 days) have been tabulated with an emphasis to achieve them as they serve as a quality indicator for care. Bacteriological conversion is now defined when 2 cultures, 7-days apart (originally 1 month) are negative. Lost-to-follow-up is now defined as interruption in treatment for more than 2 months (originally 1 month). Guidelines for prophylaxis of house-hold contacts in DR-TB have been defined- 6 months of levofloxacin for MDR-TB with FQ susceptibility, 4 months of R in H resistance and 6 months of H in RR-TB with H and FQ susceptibility, with monitoring up to 2 years for any symptoms.

5. Future directives

The diagnosis and treatment guidelines of DR-TB is still evolving, and India is updating the same in concurrence with the WHO recommendations. However, at the national level, there are various gaps including logistics, equipment, training, soci0-economic and cultural factors, which also need to be tackled. Integration of the private sector with public health services can definitely help to increase and improve the coverage and treatment of DR-TB in India. Linking the TB control programme with the Ayushman Bharat-Pradhan Mantri Jan Arogya Yojana (PM-JAY) can alleviate the economic constraints, as it can help provide free indoor care to patients. National level centres of excellence, State level difficult-to-treat TB clinics and regular training of the doctors and other supportive health care workers can help in capacity building and improving patient care and outcomes. Diagnostics must adhere to expected turn-around times. Whole genome sequencing platforms are to be made available in the national and state laboratories, to detect known and novel mutations responsible for the drug resistance patterns. Eventually, the treatment algorithms based on such platforms will need to be developed. COVID-19 pandemic has created big hurdles in DR-TB program at all levels, but intensive implementation of the updated PMDT guidelines must be ensured and continued.[7] Fearing a risk of increased morbidity and mortality,[8] COVID-19 and TB coinfection also needs to be timely evaluated[9] in all suspected cases for effective therapy and best outcomes.

Contributions

All the 3 authors contributed to –Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; & Drafting the work or revising it critically for important intellectual content; & Final approval of the version to be published; & Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of interest

The authors have none to declare.

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